REMARKS

The specification is amended at page 1 and claim 25 is amended. No new matter is added. Reconsideration of the rejection is requested.

The Examiner rejected claims 25-28 as being vague and indefinite because the full name of "FcRn" should be recited in the claim. Applicant has amended the claim to address this rejection. Withdrawal of the rejection on this basis is requested.

The Examiner rejected claim 25 on the basis that it was not clear to the Examiner what is meant by the phrase "antigen that is characteristic of a pathogen". It is believed that the Examiner has not made out a *prima facie* case for rejecting this claim and it is requested that the rejection be withdrawn. The Examiner has not articulated anything that is ambiguous about the phrase. In addition, the Examiner is directed to pages 20-25. It is believed that it would be abundantly clear to one of ordinary skill in the art what is meant by the phrase "antigen characteristic of a pathogen" upon reading these pages. Five full pages of examples are given of antigens characteristic of pathogens. Finally, the Patent Office already has approved of the use of this language in both of the related issued patents, U.S. Patent 6,086,875 and 6,030,613. It is believed that the Office should not act inconsistently in these cases and raise issues that previously have been reviewed.

The Examiner rejected claim 26 on the basis that the term "non-specific IgG" is vague and indefinite because it has not been defined in the specification. It is requested that this rejection be withdrawn. The term "non-specific IgG" is one which is quite familiar to those of ordinary skill in the art, having been used for at least thirty years. The properties and methods of preparation of non-specific IgG are well-known. In addition, the Patent Office already has approved of the use of this language in both of the related issued patents, U.S. Patent 6,086,875 and 6,030,613. It is believed that the Office should not act inconsistently in these cases and raise issues that previously have been reviewed.

The Examiner rejected claim 26 on the basis that the term "FcRn binding fragment of IgG" is vague and indefinite. It is requested that this rejection be withdrawn. The Examiner is directed to page 14 of the application, lines 4-22 and also to page 14, lines 23-page 15, line 14. The Examiner will see that the fragments of IgG which can be used are clearly described. Among them are the Fc fragment of IgG "and other fragments of IgG that include the complete binding region for the FcRn receptor". The binding region of the Fc portion of IgG that binds to the FcRn receptor is described. Methods for testing whether a fragment binds are described. It is believed that those of ordinary skill in the art will have no difficulty in interpreting the meaning of this phrase.

The Examiner rejected claims 25-31 and 33-34 on the basis of 35 U.S.C. §102 (b) as being anticipated by WO92/05793 (Medarex). It is requested that this rejection be withdrawn in view of the following remarks.

Before discussing the Medarex reference, applicants wish to provide the Examiner some basic information relating to the present invention, which is important to understanding applicants' position with respect to the 102 (b) and the 103 rejections.

The FcRn receptor has a different structure and function than leukocyte Fc receptors. FcRn is structurally distinct, for example, from Fc-γ antigen-presenting cells. The function of FcRn is different as well. There appears to be some confusion in the mind of the Examiner regarding the receptor of the present invention versus the receptors of the cited prior art. These differences are summarized below.

FcRn: This is the receptor to which the conjugates of the present invention are directed. FcRn is expressed on epithelial cell surfaces of adult intestinal tissue. FcRn in such adult human tissue is functional, i.e., it has the ability to mediate IgG transcytosis across the epithelial barrier in such tissue. The receptors mentioned in the cited prior art are structurally unrelated to FcRn and differ from FcRn in the cell types on which they are found and in their pathways within cells. Except for one receptor (FcγRI), these receptors also differ from FcRn in the ligands which they bind. In other words, the receptors are so different that the behavior or biological function of FcRn cannot remotely be inferred from the behavior or biological function of these other receptors.

FcεRII: This receptor is present on B cells. It is not known to be present on epithelial cells. This receptor binds IgE. It does not bind IgG. It has no known function or role in transcellular transport, and in particular transepithelial transport.

FcγRIII: This receptor is present on antigen presenting cells. It is not known to be present on epithelial cells. This receptor binds predominantly IgG complexes, but not monomeric IgG. It has no known function or role in transcellular transport, and in particular transepithelial transport.

FcγRII: This receptor is present on antigen presenting cells. It is not known to be present on epithelial cells. This receptor binds predominantly IgG complexes, but not monomeric IgG. It has no known function or role in transcellular transport, and in particular transepithelial transport.

FcγRI: This receptor is present on antigen presenting cells. It is not known to be present on epithelial cells. This receptor binds predominantly monomeric IgG but can also bind immune complexes. It binds IgG, however, at entirely different sites than where FcRn binds IgG, and it binds IgG for entirely different purposes than FcRn binds IgG. It has no known function or role in transcellular transport, and in particular transepithelial transport.

Medarex is directed to bi-specific binding agents that, on the one hand bind an antigen, and on the other hand, can target the antigen through a second binding domain to an antigen-presenting cell.

Medarex teaches that antigen antibody complexes are taken-up by receptors on antigen-presenting cells such as macrophages. The Fc receptors responsible for this according to Medarex are receptors such as Fc-γ. (These are not FcRn receptors). Medarex suggests that it is not a useful therapeutic approach to direct antigens to macrophages via antigen bound to antibodies because circulating antibody will compete for the Fc-γ receptors and will overwhelm such an approach. Instead, Medarex proposes binding-agents that have two arms, one arm which binds an antigen and another which binds an Fc-γ receptor of a macrophage, but binds it remote from the Fc-γ binding site for IgG.

> "The bi-specific binding agents specifically binds the antigen...and, at the same time, binds a surface receptor of an antigen-presenting cell which can internalize antigen for processing and presentation. The receptor-binding component of the bi-specific binding agent (and thus the bi-specific binding agent itself) binds the receptor of the antigen-presenting cell without substantially being blocked by the natural ligand for the receptor. As a result, targeting of the antigen to the receptor will not be prevented by physiological levels of the ligand and the targeted receptor will remain capable of binding the ligand and functioning."

Medarex proposes two kinds of "binding-agents". One is a "heteroantibody" and the other is a "bi-specific antibody". Medarex teaches that a heteroantibody is two separate entities covalently bound to one another. The entities can be two whole antibodies, or two fragments. If they are fragments, then they must include the variable region also must maintain their binding specificity. Medarex teaches that such fragments can be "Fv, Fab, Fab', or $F(ab')_2$. The fragments suggested by Medarex specifically do not have an FcRn binding portion; that portion has been cleaved away. When the heteroantibody is whole antibody, than the covalent conjugation is carried out without any consideration of maintaining the integrity of the FcRn binding portion of the antibody (which can be destroyed during such conjugation).

In another approach, bi-specific antibodies are proposed. Medarex teaches that bi-specific antibodies are single antibodies which possess one binding specificity on one of the binding arms and a different binding specificity on the other of the binding arms. One of the specificities would be to the antigen and the other would be to the Fc-γ receptor (again, remote from the Fc binding site of the Fc-γ receptor). It is not stated whether the various techniques for preparing such antibodies would or would not preserve the Fc binding capabilities of such an antibody.

As should be apparent from reading Medarex, most of the embodiments proposed by Medarex (and perhaps all) have no FcRn binding moiety. That portion of the molecule is unnecessary for the purposes described in Medarex.

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Applicants wish to point out what Medarex does not teach. Medarex does not teach anything about modes of delivery or pharmaceutical preparations relating thereto. There virtually is no mention of appropriate modes of delivery in Medarex. There in particular is no mention of oral delivery and oral formulations, aerosol delivery and aerosol formulations, or nasal delivery and nasal formulations. Medarex also teaches away from using non-specific IgG. Medarex, in fact, teaches the opposite. Highly specific IgG for a particular region on an Fc-γ receptor is the goal. Likewise, Medarex does not teach FcRn binding fragments of IgG. The only fragments taught by Medarex are those where the FcRn binding portion of IgG has been removed.

Applicants request that the rejection on the basis of 35 U.S.C. §102 (b) over Medarex be withdrawn. Firstly, claim 25 requires a conjugate of an antigen and "an FcRn binding partner". Medarex does not teach such a conjugate. Medarex teaches a conjugate of an antigen and an Fc-γ binding partner, which is completely different from the conjugate of the present invention. If Medarex's conjugate included an FcRn binding partner (as a result of it happening to have an intact appropriate FcRn binding portion of an immunoglubulin), then it only could have occurred, if at all, by accident. As such, that is not anticipation.

Claim 25 also includes the limitation that the pharmaceutical preparation is in a unit dosage that is an oral formulation, an aerosol formulation, or a nasal formulation. Such formulations are exemplified in the specification. No such formulations are mentioned or stated in Medarex, nor are such formulations inherent in the teachings of Medarex. These are affirmative limitations in the claims which are not shown or suggested by Medarex.

Claim 26 includes the limitation that the FcRn binding partner is non-specific IgG or an FcRn binding fragment of IgG. As discussed above, these limitations are not shown or suggested by Medarex.

Claim 27 requires that the FcRn binding partner is an Fc fragment of IgG. Again, this limitation is not shown or suggested by Medarex. If anything, Medarex teaches exactly the opposite, that is, cleaving away the Fc fragment.

Claim 29 includes the limitation that the unit dosage is an oral formulation and claim 30 adds that the formulation is a solid oral formulation, an elixir or a syrup. Nothing in Medarex shows or suggests these limitations. They are not present in Medarex, either explicitly or inherently.

Claim 31 requires that the unit dosage be an aerosol formulation and claim 32 requires that the aerosol formulation include a propellant. Nothing in Medarex shows or suggests these limitations. They are not present in Medarex, either explicitly or inherently.

Claim 33 requires that the pharmaceutical preparation be a nasal formulation. Nothing in Medarex shows or suggests this limitation. It is not present in Medarex, either explicitly or inherently.

It is believed that the rejection on the basis of 35 U.S.C. §102 (b) is improper, and it is respectfully requested that it be withdrawn in view of the foregoing remarks.

The Examiner also rejected the claims under 35 U.S.C. §103 on the basis of the combination of Medarex and Capon. Applicants believe that the rejection is improper and request reconsideration in view of the following remarks.

Capon teaches a method for increasing the half-life of "ligand-binding partners". "Ligand-binding Partners" include receptors and carrier proteins, as well as hormones, cellular adhesive proteins (proteins which direct or induce the adhesion of one cell to another), lectin binding molecules, growth factors, enzymes, nutrient substances and the like. Capon does not teach anything about or even mention vaccines and has nothing to do with inducing immune responses against antigens that are characteristic of pathogens. Capon also makes no mention of the directing or delivering an antigen to an antigen-presenting cell, which is the purpose of Medarex teaching.

Capon increases the half-life of the ligand-binding partners by conjugating them to "plasma-stable proteins". Examples of plasma-stable proteins, according to Capon, are albumin, lipoprotein, apolipoprotein, transferon and immunoglobulin, including IgA, IgD, IgE, IgM and IgG. On the entire list described by Capon, only IgG has an FcRn binding domain. Practically every embodiment described by Capon would not work according to the present invention because there is no FcRn binding moiety present.

In the entire Capon specification of some forty-five columns, there is one sentence which states:

> "Alternative routes include tablets and the like, commercially available nebulizers for liquid formulations, and inhalation of lyophilized or aerosolized receptors." (column 31, lines 5-8).

Capon does not state which plasma-stable proteins would be suitable for such delivery. Capon does not state which ligand-binding partners would be suitable for such delivery (although Capon mentions receptors in connection with lyophilization or aerosolization). Capon does state, however:

"Intravenous delivery or delivery through catheter or other surgical tubing will be the primary route for therapeutic administration." (column 31, lines 3-5).

It is believed that the rejection on the basis of the combination of Capon and Medarex is improper. Firstly, it is believed that these two references are not properly combined. Secondly, even if they were combined, Capon does not supply those elements of the claims missing from the Medarex reference.

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Medarex teaches that the Fc portion of IgG is appropriately eliminated from the Medarex molecules. The Examiner suggests that it would be obvious to put back on the very portion of IgG which Medarex suggests is appropriate to eliminate. The combination on its face is improper because Medarex teaches away from the combination.

The combination also is improper because it is based on hindsight reasoning. Capon has nothing to do with the subject matter of the Medarex application and it is only through hindsight picking and choosing of isolated aspects of Capon that the Examiner can arrive at the combination which would purport to render obvious the present invention. There would be no motivation to one of ordinary skill in the art reading Medarex to even look to Capon, let alone to pick and choose some isolated aspect of Capon and reconstruct the Medarex molecules with this isolated aspect to meet limitations of the claims of the present invention. Medarex relates to vaccines and targeted delivery of antigens to antigen presenting cells. Medarex does not raise or suggest any problems relating to half-life for antigen presentation to cells such as macrophages. Capon does not relate to vaccines and does not relate to targeting of antigens to antigen-presenting cells. Capon relates to increasing the half-life of molecules that are not vaccines. Capon describes numerous molecules that can be used for this purpose. All but one of these would not work according to the present invention as all but one do not have an FcRn binding domain. There simply is no motivation to make the combination suggested by the Examiner.

In addition, even if one were to combine these two references as suggested by the Examiner, such a combination would not result in the invention. Capon has no definitive teaching whatsoever about the circumstances under which it would be appropriate, if any, to prepare an oral formulation, a nasal formulation or a pulmonary formulation. The vague reference by Capon to the possibility of such a delivery mode is not sufficient to render obvious the present application's specific teaching about specific formulations for specific kinds of conjugates. There is nothing in Capon to suggest that it would be obvious to deliver the vaccine preparations of Medarex in an oral format, a nasal format or an aerosol format. Capon does not even speak to vaccines. Capon does not suggest that the addition of the plasma-stabilizing protein enhances or permits such delivery. To the contrary, Capon simply imagines standard modes of delivery.

Applicants also note the Examiner's comments at page 4 of the Office Action. In particular, the Examiner states that the Capon patent teaches a pharmaceutical preparation comprising "an antigen conjugated to an Fc fragment of IgG". Respectfully, the Capon patent does not relate to antigens at all.

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The Examiner also states that Capon teaches that the pharmaceutical preparations are useful for the treatment of individuals "in need of antiviral therapy". While this may be true, Capon does not teach antigen-based antiviral therapy or any antigen-based therapy.

Finally, the Examiner mentions that the specification "discloses the well-known fact that the FcRn is present in epithelial tissue of human children and adults (page 7, lines 2-3)". Respectfully, this teaching is in the Summary of the Invention. This was not a "well-known fact". Instead, the discovery of this fact is the basis of the invention. It is improper to rely on a teaching in the specification for rejecting the claims.

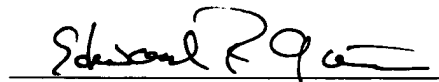
The Examiner has relied on these statements in framing the rejections of the claims. The rejection on the basis of 35 U.S.C. §103 should be withdrawn for these reasons as well.

The Examiner rejected claims 25-34 provisionally under 35 U.S.C. §102 (e) as anticipated by co-pending application 08/578,171. This application has been abandoned and it is believed that the provisional rejection no longer is proper. A similar rejection was made under the judicially created doctrine of obviousness-type double patenting. Because the '171 application has been abandoned, it is believed that this rejection should be withdrawn.

Finally, the Examiner made mention that there could be a basis of a rejection under 35 U.S.C. §103 (a) (based upon the '171 application), if the '171 case qualified as prior art under 35 U.S.C. §102 (f) or (g). It is not believed that the '171 abandoned application qualifies as prior art under either of these sections and it is not believed that any further action is necessary.

Applicants request an interview with the Examiner to advance the prosecution of this case. A Notice of Allowance is respectfully requested.

Respectfully submitted,



Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 720-3500

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